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Evaluating the Risks and Benefits of Phase II and III Cancer Clinical Trials:

A Look at Institutional Review Board Members in the Netherlands

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The Declaration of Helsinki and other national and international regulations oblige Institutional Review Boards (IRBs) to weigh the risks of medical research against its benefits, and to assess the ratio between the two. In the Netherlands, the Medical Research Involving Human Subjects Act (WMO) states that a review committee may only approve a research study when "it is reasonable to expect that the risk to and burden for the subject will be in proportion to the potential value of the research."[1] In order for a study to be approved, this risk-benefit ratio must, in the IRB's opinion, be "favorable," "in balance," or "proportional." This assumes that IRBs are sufficiently aware of which risks the medical research community and society, in general, find acceptable in relation to which benefits. The extent to which this assumption is justified in practice is open to question, especially considering the vague description of this requirement in the various regulations.

The requirement for a favorable risk-benefit ratio further presupposes that IRBs know what is important to research participants with respect to their protection. Whether this assumption is justified is also unknown. For example, there are indications that patients' experiences of recruitment to early phase cancer trials and their perceptions of the informed consent process reflect a lack of understanding of the trial in which they are taking part.[2] This may be due, in part to vagueness, inconsistency, and overstatement of benefit in the consent forms for these trials.[3]

The absence of clear criteria for assessing the risk-benefit ratio has been identified as a weak link in the IRB review process.[4] Previous studies have indicated that IRB members find risk-benefit ratio assessments to be one of the most difficult tasks involved in reviewing research protocols.[5] For example, van Luijn et al., found that phase II cancer protocols provide too little information relating to the evaluation of cost-benefit and scientific issues; that IRB members felt less than fully competent in carrying out such evaluations; that only a small minority of IRB members weigh risks and benefits against each other in a systematic way, rather than intuitively; and that one-third of IRB members did not determine the risk-benefit ratio themselves, but rather preferred to leave that to the individuals being recruited for the studies.[6] The results of another study indicated that the final judgment by IRB members on a trial's ethical acceptability was significantly correlated with the assessment of the protocol's risk-benefit ratio.[7]

Little is known, however, about the kinds of difficulties IRB members experience when making risk-benefit assessments, whether they need assistance in making these assessments, and whether they think patients should participate in the IRB's assessment of risks and benefits. In this article, we report on a study that sought to determine which aspects of the risk-benefit ratio assessment of phase II and phase III cancer clinical trials individual IRB members find the most difficult, whether they require more information and education in making such assessments, how the process can be improved, and whether the participation of patients is viewed as a means of improving the quality of the assessments.[8]

Study Methods

The IRBs of six Dutch academic hospitals and two specialized cancer centers were asked by mail to participate in the study. We did not select non-academic hospitals because they do not evaluate sufficient numbers of cancer clinical trials to be appropriate candidates for such a study. Six of the eight IRBs agreed to participate, including the academic hospitals of the universities of Utrecht, Rotterdam, and Leiden, the Vrije Universiteit in Amsterdam, the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital in Amsterdam, and the Daniel den Hoed Cancer Center in Rotterdam. All members of these IRBs (N = 64) were invited to take part in the study, of whom 52 agreed to do so. One IRB member of the IRB of a fifth Dutch academic hospital also agreed to participate. The primary reason for not participating was the time-consuming nature of the research. The participating IRB members included medical specialists (41%), family physicians (8%), nurs-

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Table 1. Interview Questions

Would you like more information and education in assessing the RBR of protocols?
What kind of information and education would you like?
Do you have any suggestions that would make the RBR assessment process easier for you?
Do you believe that it is desirable for patients (who have experience as research subjects) to participate in an IRB?

es (15%), and individuals from other disciplines (36%), including four pharmacists, two ethicists, two social scientists, one statistician, and one attorney, among others. The age of the participants ranged from 28 to 69 years and the majority of respondents (64%) were male. Nine percent had served on the IRB for less than one year, 47% for between one and four years, and 44% for four years or longer.

We conducted semi-structured interviews using a combination of open- and closed-ended questions that focused on the most difficult aspects in assessing the risk-benefit ratio of phase II and phase III cancer clinical trial protocols; the perceived need for additional information and education in making this assessment; suggestions for improving the risk-benefit assessment; and the desirability of having patients participate in the IRBs' assessment of a trial's risks and benefits. The interview schedule was developed on the basis of the literature[9] and had been previously pilot tested among five IRB members or former IRB members. The first author performed the interviews at the IRB members' place of work. On average, the interview took approximately one hour to complete.

The interviews included two open-ended questions concerning the most difficult aspects of assessing the risks and benefits of phase II and phase III cancer protocols and three open-ended questions concerning the need for more information and education, and suggestions for improving the risk-benefit assessment process for these types of protocols. One closed-ended question concerned the desirability of having patients participate in the IRBs' assessment of the risk-benefit ratio (Table 1). Responses were scored on a 4-point Likert scale from 1 (very desirable) to 4 (not desirable at all). Respondents were asked to describe the reasons underlying the responses that they provided to the question.

Open-ended questions were organized into categories and are reported as percentages. The categories were not always mutually exclusive, as respondents could, for example, mention more than one difficult aspect of the assessment of the risk-benefit ratio (Table 2), type of support needed (Table 3), or suggestion for improving the IRB's risk-benefit ratio assessments (Table 4). Responses are illustrated in the text with salient statements made by IRB members.

Descriptive statistics were calculated for responses to the closed-ended question. Chi-square statistics were used to test whether the background characteristics of the IRB members (e.g., age, gender, professional background, years of experience on IRBs) were associated significantly with perceived need for information and training, and attitudes towards patient membership on an IRB.

Results

As reported in Table 2, making risk-benefit ratio decisions without clear criteria and in the face of uncertainty with regard to patient benefits and study rationale were

Table 2. Opinions of IRB Members Concerning the Most Difficult Aspects of Assessing the Risk-Benefit Ratio of Phase II and Phase III Cancer Trials (n=53)

	Phase II	*Phase III*
Lack of criteria to assess the risk-benefit ratio	62%	39%
Uncertainty about the benefits to patients and the study's rationale	41%	37%
Doing research/confronting patients with difficult choices in the face of necessary risks	15%	0%
Gaining a view of all relevant factors	12%	2%
Withholding treatment because of placebo	0%	10%
Various other aspects	21%[a]	27%[b]

a. e.g., No feedback on study results, therefore it remains unclear whether the estimation and evaluation of risks and benefits was correct; communication with other IRB members about the RBR; the researchers' reaction if the protocol is rejected

b. e.g., No feedback on study results; uncertainty about toxicity; the perhaps unrealistic hope that is provided to patients by letting them participate in the study;

Note: The percentages do not total 100% because more than one response could be given.

Table 3. Type of Information and Education Desired by IRB Members in Assessing the Risk-Benefit Ratio of Phase II and III Cancer Clinical Trials (n=30) [a]

Courses or seminars	52%
Feedback on patients' trial experiences and trial results	32%
Reflection on past decisions/overview of new developments in oncology research	8%
Various[b]	36%

Note: The percentages do not total 100% because more than one response could be provided.

a. Only IRB members who said that they needed more knowledge and education answered this question.
b. Including: risk-benefit assessment by researchers; methodological aspects; how to apply general ethical concepts to particular protocols; guidelines about how to assess the RBR; feedback on individual IRB performance; more training in legal matters and animal research; a list with important things to think about for every member.

perceived as the two most difficult aspects of the process of assessing the risk-benefit ratio for phase II and III cancer trials. Specific issues mentioned by respondents during the interview included difficulty in comparing risks with benefits, inadequate knowledge of the acceptability of certain risks, and an inability to imagine the impact of a failed clinical trial-based treatment on the patient/subjects.

Fifty-six percent of the IRB members reported that they would like to receive more information about and education in assessing the risk-benefit ratio of protocols. As indicated in Table 3, approximately half of the respondents who expressed interest in receiving more information or training favored courses or seminars, and one-third indicated a desire to obtain feedback on trial results and on the experiences of patient/subjects who participate in trials. The remaining IRB members (44%) expressed no desire for additional training or assistance in how to assess the risk-benefit ratio of protocols, as they believed that the IRB meetings themselves provided sufficient training opportunities and sources of information.

As shown in Table 4, more than half of the IRB members reported wanting more information, particularly relating to patients' perceptions of the risks and benefits involved with clinical trials. Approximately one-quarter of the respondents reported that it would be helpful if investigators provided IRB members with their own assessment of a study's risk-benefit ratio. Additional training and the use of a checklist in order to review all of the major issues involved in assessing a study's risk-benefit ratio were also mentioned as possibly helpful in facilitating the IRB's review process.

The majority of respondents (54%) opposed the idea of having patients (who have experience as research subjects) participate on the IRB (Table 5). Those who rejected this proposal did not believe that patients had any specific contribution to make, were concerned that open discussions would be hampered, believed patients would make judgments solely on the basis of their own personal experiences, or felt that participation on an IRB would simply be too difficult or would impose too great a burden on patients. Still others believed that the logistics would be difficult because different patients would be needed for different protocols, or that it would be difficult to find a single patient who could represent the diverse population(s) of patients.

Twenty-three percent of the IRB members considered it desirable to have patients on IRBs, and the remaining 23% expressed no opinion. Most of those favoring patient participation considered patients to be "experiential experts" who could inform other IRB members about the meaning of risks and benefits.

Table 4. IRB Members' Suggestions for Improving the Risk-Benefit Assessment of Phase II and III Cancer Clinical Trials (n=53)

More knowledge available on trial experience/ risk-benefit perceptions of patients	56%
Risk-benefit assessments by researchers	26%
Additional training and checklists for IRB members	23%
More time for preparation and discussion/ contact with researchers	9%
Improvement of IRB discussions	7%
Various	28%

Note: The percentages do not total 100% because more than one suggestion could be given.

Table 5. IRB Members' Opinions About the Desirability of Having Patients Participate on IRBs (n=53)

Patient participation on IRBs is desirable	23%
Patient participation on IRBs is not desirable	54%
Don't know/no opinion	23%

Others believed that patients are better able to evaluate the quality of written patient information than other IRB members.

Significantly fewer oncologists believed that they could benefit from more information and education than did other professionals (18% versus 62%; $p < .05$). No statistically significant associations were found between duration of IRB membership, age or gender and the perceived need for more information and education. Relatively new IRB members (those with four or fewer years of experience on an IRB) were significantly more likely to favor patient participation on IRBs than were members with more experience (38% versus 4%; $p = .02$). Although not statistically significant, fewer physicians than other professionals favored having patients as members of IRBs (12% versus 35%). Finally, significantly more female than male IRB members were opposed to having patients serve on IRBs (72% versus 44%; $p = .02$).

Discussion

The objective of this study was to obtain insight into the IRB process of assessing the risk-benefit ratio of phase II and III cancer clinical trials as experienced by individual members of IRBs. We first sought to identify the most difficult aspects of the risk-benefit assessment of phase II and III protocols. The lack of criteria for assessing the risk-benefit ratio, the uncertainty concerning the benefits to patients, and the study rationale were reported as the most difficult aspects of the assessment process. Other studies have also found a lack of clear criteria for evaluating a trial's risk-benefit ratio and IRB members' lack of technical expertise necessary for weighing the risks and benefits against each other to be major problems.[10]

Second, we investigated the needs expressed by IRB members for more information and education in assessing the risk-benefit ratio of phase II and III cancer protocols and their suggestions for improving their own assessments. Most respondents reported that additional information and education would be welcome. Although courses are available for IRB members in the Netherlands, they are not mandatory and only a small percentage of members attend them.

The IRB members made a number of suggestions regarding possible ways to improve the assessment of the risk-benefit ratio of phase II and III cancer protocols: receiving more information about patients' trial experiences and risk-benefit perceptions; receiving researchers' assessment of the risk-benefit ratio; and providing checklists and more training facilities for IRB members.

The findings of our study indicate that IRBs know little about the perceptions and experiences of patients regarding the risks and benefits of research participation. In addition, the findings suggest a striking tension in IRB members' apparent lack of insight into the patient perspective (i.e., the *meaning* of the risks and benefits to patients) and their actual task (protecting human subjects against medical research that carries too many risks). This also suggests that, to be able to assess the risk-benefit ratio of a study (i.e., to have criteria for weighing risks and benefits against each other), more knowledge of the patients' perspective is needed. Such information may then become part of a broad mix of factors that IRBs consider in assessing a study's risk-benefit ratio. When IRBs know how patients have experienced participation in trials comparable to the study in question, it may be possible for IRB members to make a comparison between their own perceptions of risks and benefits and those of the patients. IRBs can then take the patients' perspective—beyond their own perceptions—into consideration in order to improve their assessment of the risk-benefit ratio.

To determine whether their decision to approve a research protocol is ethically justifiable, IRB members must imagine the consequences of their decision for patients.[11] However, because it is impossible to know how others will actually assess these consequences, IRB members can only make a rough estimate of what their decisions will mean to others.[12] Risk-benefit assessments depend on the relative importance of the various factors to be weighed. More insight is needed, therefore, into the experiences, as well as the values and goals, of patients if IRBs are to be capable of determining the importance of the factors and if risk-benefit criteria are to be well chosen.[13] It is important to emphasize, however, that the desire for more information about the patients' perspective should not be equated with the common but mistaken view that a study's risk-benefit ratio is acceptable if patients want to enroll. The consent of the patient to become a research subject is an essential, but second moral requirement. The first moral requirement for research is that the risk-benefit ratio be assessed and found acceptable, as has been stated earlier. This is important to recognize, because individual

patients are prepared to take significant risks for small chances of benefit. Thus we would emphasize that the relevant patient role is as patients/subjects, reflecting experiences in research, but not necessarily values. How patients view their chances of benefit should not affect the assessment of a study's risk-benefit ratio. The question whether perceptions of risks and benefits by potential trial participants (their "values" or "preferences") should affect this assessment is a complicated one, because the assessment must take place against the backdrop of the alternatives to research participation that are available to patients; in oncology, those may be dismal. This issue should be one focus of future empirical and conceptual research.

Third, we asked IRB members about the desirability of having patients participate in the review of research protocols. Experiences with patients reviewing AIDS protocols have been positive.[14] Others have found that patients' estimate of the severity of certain risks differs considerably from that of physicians and nurses.[15] Nevertheless, although the respondents in our study indicated that their risk-benefit assessments might be improved by having more insight into the patients' perspective about research risks and benefits, less than a quarter were in favor of having patients participate on IRBs. Of course, it makes a difference whether the patients are potential participants in the trials reviewed or patients who have experience as research subjects. These two patient groups have very different things to bring to the IRB table. There may be considerable differences in the values and feasibility of patients' inclusion on an IRB devoted to oncology research in comparison to a general medical IRB (since many IRB members, lay or otherwise, have considerable experience as patients).

Finally, we investigated the association between IRB members' background characteristics and their views. Not surprisingly, fewer oncologists expressed the need for more information and education in making risk-benefit assessments than did other professionals. Female IRB members and those who had been involved in IRBs for a longer period of time tended to be less favorable toward having patients participate on IRBs, though it is unclear why this is so. Although most nurses in this study were female, there were also many females from other professions, and being a nurse had no significant relationship with attitudes towards patient participation on IRBs.

The results must be interpreted in light of certain limitations of the study. First, the study did not distinguish among the various types of phase II and III protocols (e.g., chemotherapy, radiotherapy, or surgery). While there is no reason to believe that this would have a significant impact on the findings, it could be investigated in future studies. In addition, respondents were not asked to distinguish between protocols arising from within their own institutions and those from other sources (either national or international). Unfortunately, we could not obtain systematic data on this matter from the participating IRBs because such information is not routinely collected. Additional research is needed, therefore, to determine whether the perceived difficulties associated with assessing the risk-benefit ratio of protocols and the need for information and education vary significantly as a function of the protocol's origin (i.e., local versus national or international; academic versus industry)

We also note that the focus of our research was on the individual members of IRBs. The decisions made by IRBs as a whole, and the discussions that form the basis of such decisions, are of a collective nature. Each IRB member contributes to the decision-making process from a unique professional perspective, and the whole is undoubtedly more than the sum of its parts. A more dynamic, group-oriented research approach is also needed to obtain a more comprehensive picture of the issues surrounding risk-benefit assessments. In a future paper, we will report the results of a later stage of our research in which such group dynamics were investigated. At the same time, we would emphasize that each IRB member brings his or her own perspective to such deliberations, and is expected to be well prepared to participate actively in the decision-making process. Thus it is not inappropriate to examine the attitudes and behavior of individual IRB members.

The results of the current study point to an intriguing paradox. On the one hand, the absence of clear criteria and the perceived uncertainty about the benefits to patients and the rationale for specific clinical trials make assessment of the risk-benefit ratio of phase II and III cancer trials difficult—apparently so difficult that most IRB members would like to receive additional information and education in making such an assessment (e.g., learning from past experiences by providing feedback on trial results or past decisions by IRBs). Additionally, most IRB members believe that additional insight into the experiences and perceptions of patients would help improve the assessment process. On the other hand, the majority of the surveyed IRB members were opposed to having patients participate on IRBs. We believe that before systematically excluding patients from IRB participation, empirical research is needed to investigate the effects, both positive and negative, of having patient participation on IRBs. Studies are also needed about patients' research experiences and perceptions of the risks and benefits of clinical trials.[16] Both lines of research could contribute meaningfully to better understanding of the risks and benefits of research participation and to improving the assessment of the risk-

benefit ratio of phase II and III cancer clinical trials.

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8. Phase II and III cancer clinical trials both study questions of therapeutic effect. Phase II trials, typically involving a limited number of patients, address the question of whether a new therapeutic agent or treatment has an antitumor effect. Phase III clinical trials are typically larger in size and randomize patients between a standard and an experimental treatment.

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